REMARKS

Claims 11, 19-27, and 30-33 are pending in the application and are under active consideration. Claims 12-18 and 29 are canceled herein without prejudice or disclaimer.

Claim 11 has been amended to make explicit that the HCV antigen is an E1/E2 heterodimer. Support for the amendment can be found in the original claims and the specification, for example, at page 8, lines 34-35.

Claims 19-27, 31, and 33 have been amended to remove dependency on canceled claims and to clarify antecedent basis.

The present amendments do not introduce new issues, and place the subject application in condition for allowance and/or simplify issues for appeal. Accordingly, entry of the amendments after final is respectfully requested.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Rejection under 35 U.S.C. § 103

Claims 11-27 and 29-33 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Ralston et al. (WO 92/08734; hereinafter "Ralston") in view of Casey et al. (U.S. Patent No. 5,667,992; hereinafter "Casey"). In maintaining the rejection, the Final Office Action dismisses the Declarations of David Chien and Michael Houghton (Final Office Action, page 5). The Final Office Action asserts that "both declarations and Applicants' arguments fail to address the primary reference, Ralston, which describes a method for diagnosing (which encompasses the claim limitation of 'detecting') HCV by contacting body component with a purified native form (which encompasses a non-denatured form) of HCV E1 or E2, or E/E2 aggregate antigen in an immunoassay (which encompasses the claim limitation 'said contacting is performed under conditions that allow an immunological reaction to occur, whereby detectable antibody/antigen complexes are formed')" (Final Office Action, page 6). The Final Office Action further alleges:

> Even though Ralston et al. do not expressly disclose detecting the presence of HCV within the host within the first six months of infection, Ralston disclose the same process and the same use as the claimed method of HCV antibody detection using non-denatured or native form of HCV proteins, E1, E2, or E1/E2. The sensitivity of the non-denatured E1 or E2 antigens to detect HCV in individuals infected with HCV for less than six months is a new advantageous property of a prior art process disclosed in Ralston. Newly discovered property of prior art cannot support patent on that same art. (Final Office Action, page 7.)

Applicants respectfully traverse the rejection and the Office's purported facts underlying the rejection on the following grounds.

The recent decision by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007) reaffirmed the viability of the four factual inquiries underlying an obviousness analysis provided in *Graham v. John Deere*, 148 USPQ 459, 467 (U.S. 1966). These factors include: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations. Moreover, the Supreme Court in *KSR* recognized that the "teaching, suggestion, or motivation" analysis provides a helpful insight in determining whether the claimed subject matter is obvious. This analysis is provided in MPEP 2142. In particular, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Both the teaching or suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art, not in applicant's disclosure. See, e.g., *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Based on the foregoing, applicant respectfully submits the Office has failed to establish a *prima facie* case of obviousness.

The Office has failed to provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." *KSR*, page 13. In fact, the evidence is to the contrary. The cited art fails to provide evidence that an E1/E2 heterodimer purified under non-denaturing conditions would be especially effective in detecting HCV in a mammalian host within the first six months of HCV infection. The primary reference of Ralston

fails to describe or suggest an immunoassay using an E1/E2 heterodimer as an immunoassay reagent. On the contrary, Ralston describes only the use of E1 or E2 separately in immunoassays (see Ralston at page 4, lines 10-14).

Nor does the secondary reference of Casey describe or suggest using an E1/E2 heterodimer. All of the immunoassays performed by Casey used E1 or E2 antigens separately. Applicants again emphasize that Casey does not teach or suggest the use of non-denaturing conditions in order to preserve conformational epitopes of E1 and E2. Rather, Casey describes a method of preparing cell lysates containing E1 or E2 fusion proteins using the denaturing detergent, sodium dodecyl sulfate (see col. 13, lines 19-25) and describes methods of freezing and thawing cell lysates that would result in protein unfolding. Therefore, the denatured E1 and E2 antigens of Casey are unlikely to form an E1/E2 heterodimer, as recited in the current claims.

As explained in the Declarations of David Chien and Michael Houghton, it is not readily predictable what the effects of altering the antigen will be on early detection of HCV infection in subjects. An HCV E1/E2 heterodimer purified under non-denaturing conditions is expected to display different epitopes than the separate E1 and E2 antigens or denatured antigens displaying linear epitopes. In the E1/E2 heterodimer, for example, buried residues at the dimer interface and changes in the conformation of E1 and E2 caused by association in a complex alter the exposure of residues on the protein surface. Thus, there can be no reasonable expectation of success that the use of an E1/E2 heterodimer, which was not used in any of the cited references, would be effective in detecting HCV antibodies within the first 6 months of infection, and the claimed invention is therefore not obvious.

Moreover, the E1/E2 heterodimer is especially effective for detection of early HCV infection. In particular, the present application demonstrates that the E1/E2 heterodimer is more effective than E2 alone for some patients (see specification, *e.g.*, Table 2 at page 30).

Applicants again emphasize that the reactivity of E1/E2 conformational epitopes from purified non-denatured proteins with sera from HCV infected subjects could not have been predicted from a combination of Ralston and Casey. Furthermore, the present application demonstrates that immunoassays utilizing HCV envelope antigens, produced under non-denaturing conditions that allow retention of native conformational epitopes, are more effective for detecting anti-HCV antibodies within the first six months of infection as compared to the

corresponding denatured antigens (see, *e.g.*, Table 3 at page 32, which compares results with native versus denatured antigens in detection of early HCV seroconversion antibodies in sera from HCV infected patients).

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicant submits that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

Marcella Lillis, Esq.
Novartis Vaccines and Diagnostics, Inc.
Intellectual Property – R338
P.O. Box 8097
Emeryville, CA 94662-8097

Respectfully submitted,

Date: July 26, 2007

By: Jenny Buchbinder

Jenny Buchbinder, Ph.D.
Registration No. 48,588
(650) 354-3383

Novartis Vaccines and Diagnostics, Inc.
Intellectual Property – R338
P. O. Box 8097
Emeryville, CA 94662-8097